AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph on page 8, lines 27-32, with the following amended paragraph:

"This invention provides non-human mammalian models of spontaneously developing autoimmune disorders, such as organ-specific or tissue-targeted autoimmune disorders, e.g., inflammatory arthritis. These models may be generated as described herein. These mammalian models of autoimmune disorder find use in research, and for diagnostic, therapeutic and prophylactic purposes, such as the identification of crucial biomarkers that ~~participate/predict~~ participate in or predict disease progression."

Please replace the paragraph on page 12, lines 3-19, with the following amended paragraph:

"The term "autoimmune disorder or disease" as used herein refers in one embodiment to inflammatory arthritis. The Examples below describe models of an inflammatory arthritis similar to human rheumatoid arthritis that consists of one or more of the following symptoms, without limitation, inflamed joints with bone resorption, mononuclear cell infiltrates and pannus formation, bone erosion, bone remodeling, vasculitis, interstitial pneumonitis in the lung, anti-nuclear antibodies in serum, and weight loss, and further includes increased severity in females. Still other autoimmune disorders that may develop in models of this invention include other symptoms that are listed in the clinical diagnosis of autoimmune disorders such as Crohn's disease, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosis, inflammatory bowel disease, nephritis, autoimmune thyroiditis, reactive arthritis, ankylosing spondylitis, scleroderma, polymyositis, dermatomyositis, psoriasis, Wegener's granulomatosis, ulcerative colitis, Sjogren's syndrome, sarcoidosis, insulin dependent diabetes mellitus

(IDDM), as well as collections of symptoms that resemble any of the above-listed disorders. Additionally, tissue-targeted ~~autoimmmune~~ autoimmune diseases include autoimmune diseases in which disease develops selectively in a single tissue, e.g., joints or lungs, among other disorders."

Please replace the paragraph on page 15, lines 18-25, with the following amended paragraph:

"The mating of two such transgenic animals produces progeny ~~tha2t~~ that inherit the above-described transgenes by Mendelian inheritance. Progeny that co-express the TCR and the selected peptide are selected and identified by conventional means. As one example, the polymerase chain reaction technique can be employed with primer sequences that can hybridize to portions of the HA gene and MHC promoter and to the TCR sequence to detect the presence of these essential nucleotide sequences in progeny. Progeny so selected develop an autoimmune disorder, e.g., inflammatory arthritis and symptoms similar to human rheumatoid arthritis."

Please replace the paragraph on page 16, lines 13-24, with the following amended paragraph:

"Following this method, intermated progeny of other pairs of TCR expressing animals with other animals expressing a low or high-affinity agonist of the TCR produce resulting progeny that develop an autoimmune disorder. In another embodiment, this method may also be employed to produce systemic inflammatory responses affecting multiple tissues and organ systems in the animals. Such system responses may be seen in up to 15% of the progeny. In still another embodiment, tissue-targeted or tissue-specific autoimmune disorders are produced at about 85% of the progeny, e.g., joints, lungs and other tissues, depending upon the TCR and peptides employed in the method. In still another embodiment the method produces tissue-targeted ~~autoimmmune~~ autoimmune

disease resembling rheumatoid arthritis as a manifestation of a systemic anti-self immune response."

Please replace the paragraph on page 22, line 25-page 23, line 2, with the following amended paragraph:

"A nucleic acid molecule expressing the above-defined transgenes is introduced into a parent cell. As described above, the elements of the nucleic acid molecule encoding the transgenes and the identity of the parent cell may all be selected by one of skill in the art. By "introducing" the nucleic acid into the cell is meant delivering the nucleic acid molecules to the cells in any manner known to one in the art, including, without limitation, transfection, infection, electroporation, ~~sonopoation~~ sonoporation, liposome delivery, membrane fusion techniques, high velocity DNA-coated pellets, viral infection and protoplast fusion, or particle bombardment. However, other methods known by those skilled in the art may be utilized."

Please replace the paragraph on page 23, lines 7-19, with the following amended paragraph:

"The above-described transgenes and nucleic acid molecules, ~~its~~ their various components parts and the recombinant cells described above may be constructed recombinantly using conventional molecular biology techniques, site-directed mutagenesis, genetic engineering or PCR, and the like by utilizing the information provided herein. For example, methods for producing the above-identified modifications of the sequences include mutagenesis of certain nucleotides and/or insertion or deletion of nucleotides, or codons, thereby ~~effecting~~ affecting the polypeptide sequence by insertion or deletion of, e.g., non-natural amino acids. Such methods are known and may be selected by one of skill in the art. Similarly, methods for producing plasmid, other non-viral vector constructs or viral vector constructs encoding the TCRs, binding

peptides, and/or any other molecules used herein are well-known in the art, as are methods for using expression systems to produce the proteins."

Please replace the paragraph on page 27, lines 1-8, with the following amended paragraph:

"Indeed more TS1 T cells co-expressing the 6.5 TCR and endogenous ~~TCR □~~ TCR α-chains underwent division following adoptive transfer into HACII than HA104 mice, reflecting the increased potency of the S1 peptide. However, even if the effector function(s) of the autoreactive CD4+ T cells that cause inflammatory arthritis in TS1xHACII mice depends on co-expression of dual ~~TCR □~~ TCR α-chains, the activation of these cells is critically dependent on the expression of the target peptide for the 6.5 TCR (i.e. the S1 peptide) directly by APCs, since these effector functions do not become activated in TS1xHA104 mice."

Please replace the paragraphs on page 42, lines 9-22, with the following amended paragraphs:

"The levels of total serum IgG in the different mice paralleled the activation status of their APCs. As shown in FIGS. 6A-6E, serum IgG levels were elevated 8.1- and 2.6-fold, respectively, in TS1xHACII and TS1xHA104 mice relative to TS1 mice. Although total IgG levels were higher in sera from TS1xHACII mice, the levels of HA-specific IgG antibody were lower than in TS1xHA104 mice. As previously demonstrated, the high levels of HA-specific serum IgG in TS1xHA104 mice demonstrate that the 6.5+ CD4+ T cells that are present provide cognate help for HA-specific B cells that evade deletion (Reed *et al.* 2000, cited above). The reduced levels in TS1xHACII mice likely reflect more efficient deletion of HA-specific B cells induced by expression of HA on developing B cells in the ~~BM.~~ BM.

Sera from TS1xHACII mice ~~was~~ were also examined for the presence of antibodies to self-antigens that have previously been associated with inflammatory arthritis (FIGS. 6A-6D). TS1xHACII mice did not contain elevated levels of serum

antibody to IgG (rheumatoid factor), collagen II or GPI, indicating that these anti-self specificities are not required for the development of inflammatory arthritis."

Please replace the paragraph on page 43, lines 17-27, with the following amended paragraph:

"In a further phenotypic analysis, ankle thickness and weight were measured in more than 8 week-old mouse models, in which ankle ~~thinkness~~ thickness results from the development of inflammatory arthritis. As shown in the results of FIG. 8, TS1xHA104 mice are used as control mice that do not develop arthritis. The majority of the TS1xHACII mice exhibit ankle widths greater than the 95% prediction interval for TS1xHA104 mice. The age-matched cohort of TS1(SW)xHACII mice show only 4 mice exhibiting significant ankle swelling indicative of the development of inflammatory arthritis as evidenced by immunohistochemical analyses of the joints. These data show that the overall avidity of the CD4+ T cell response to the S1 peptide can determine the degree of penetrance for inflammatory arthritis in these mouse models."